Trends in Genetics

CellPress

Review

Role of genetic architecture in phenotypic plasticity

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Phenotypic plasticity, the ability of an organism to display different phenotypes across environments, is widespread in nature. Plasticity aids survival in novel environments. Herein, we review studies from yeast that allow us to start uncovering the genetic architecture of phenotypic plasticity. Genetic variants and their interactions impact the phenotype in different environments, and distinct environments modulate the impact of genetic variants and their interactions on the phenotype. Because of this, certain hidden genetic variation is expressed in specific genetic and environmental backgrounds. A better understanding of the genetic mechanisms of phenotypic plasticity will help to determine short- and long-term responses to selection and how wide variation in disease manifestation occurs in human populations.

Introduction

Natural populations are highly variable in their genetic makeup, and their ability to exhibit a given phenotype is subject to their genetic makeup and the environment. The dependence of phenotype on genetic and environmental factors is the basis of natural selection [1]. In an invariable environment, the total phenotypic variation observed results from the genetic differences among the individuals of a population [2]. When the environment is variable, the individuals with the ability to survive or adapt to these fluctuating environmental conditions persist, whereas others perish. A population of such adapted individuals can show an ability to survive across constantly changing environments and, thus, is considered to display **phenotypic plasticity** (see Glossary) [3]. In contrast, **phenotypic buffering** occurs when the individuals in a population express a constant phenotype regardless of genetic and environmental changes [4–6].

The effect of causal loci to drive phenotypic plasticity or buffering is subject to perturbations in a population's genetic and environmental backgrounds [4]. A locus modulates phenotypic plasticity if it exhibits highly variable phenotypes whenever the genetic context or the environment changes (Figure 1, Key figure) [3,7]. In contrast, if a causal locus results in similar phenotypes, the locus modulates a buffered phenotype despite the genetic context and environmental changes [4,6]. Thus, plastic and buffered outcomes depend on the genetic and environmental contexts and the selection pressures on an individual. For example, the protein-folding chaperone Hsp90 modulates phenotypic plasticity and buffering subject to genetic and environmental backgrounds [8–11]. In populations that have not undergone selection pressure, such as *in vitro* generated **segregant** populations or mutation accumulation lines, Hsp90 promotes phenotypic plasticity. In contrast, in natural populations that have undergone evolution under various selection pressures, Hsp90 buffers phenotypic variation [12].

Adaptation, the ability of organisms to survive and reproduce despite dynamic environmental changes and genetic background changes due to spontaneous mutations, is possible only if the organisms meet the fitness thresholds required for their survival [13,14]. Phenotypic plasticity

Highlights

The ability of a locus to display variable magnitudes of phenotype in different genetic and environmental contexts is known as 'phenotypic plasticity.' In contrast, phenotypic buffering happens when a locus displays an invariable phenotype.

Phenotypic plasticity or buffering is the intrinsic phenomenon of all organisms that drive evolution by modulating the adaptation of populations to environments. At the genetic level, phenotypic plasticity and buffering are modulated by the varying allelic frequencies, the release of cryptic genetic variation, the rewiring of genetic networks, and gene–environment interactions.

Despite fine-mapping genome studies, an accurate phenotype prediction from genotype is difficult due to the nonlinear relationship between genotype and phenotype. Thus, it is imperative to account for the nongenetic contributors via multiomic data to predict the phenotype better.

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can facilitate adaptation in variable environments in nature and thus has the potential to aid in selection in these varying environments [14–19]. Phenotypic plasticity not only is relevant in adaptive capabilities but also is one of the significant phenomena driving diseases such as cancers, multidrug-resistant microbes, etc. Hence, it is timely to understand the mechanisms by which phenotypic plasticity is manifested and inherited through lineages of unicellular and multicellular populations. Because heritable phenotypic changes over several generations drive evolution, it is necessary to discern the long-term effects of genotype on the phenotype. Due to the short generation time and several quantifiable phenotypes, the budding yeast *Saccharomyces cerevisiae* is one of the best organisms in which to study these phenomena. Several studies exploit polymorphisms in segregant and natural yeast populations to study the regulation of phenotypic plasticity [20–27]. These studies identify loci that directly modulate the phenotype with little dependency on the genetic background (additive loci) and the loci that interact with other loci (nonadditive loci), often forming genetic networks to modulate the phenotype. This review discusses the different types of causal genetic loci – additive, dominant, and epistatic – that contribute to the phenotype and how genetic and environmental factors interact to contribute to phenotypic plasticity in individuals and yeast populations.

Different ways in which causal loci can affect the phenotype

A phenotype is the sum of complex interactions of causal genetic loci with its genetic background and the environment [21,22,28]. Causal genetic loci may act independently through additive genetic effects or via intra- or interlocus genetic interactions leading to the nonadditive effects (dominance and epistatic effects) on the phenotype. Here we discuss ways to identify additive and nonadditive loci in individual strains and populations and their roles in phenotypic plasticity.

Additive effects

The majority of phenotypic variance is contributed by additive genetic loci [22]. At the gene level, additive loci can often be identified by studying single-gene deletion effects on the phenotype (Figure 1A) [29]. But the impact of genetic polymorphisms cannot be identified using gene-deletion studies. Therefore, additive loci can be identified by studying the association of genetic polymorphisms on the phenotype by allele-replacement strategies, wherein the effects of multiple genetic variants of a locus can be studied in constant genetic and environmental backgrounds [26,30,31]. High-throughput CRISPR-Cas9-mediated gene editing and phenotyping allows the screening of multiple genetic variants responsible for modulating the phenotype [32].

In populations, additive effects can be observed as changes in the phenotype due to alterations in allelic frequencies of the causal loci [21]. These loci can be identified by sequencing followed by genome-wide association studies or marker-based **quantitative trait locus (QTL)** mapping studies. Most yeast mapping studies, often performed in biparental segregant populations, identify multiple additive QTLs contributing to phenotype in a particular environment [22,27,33–35]. The **effect size** of an additive QTL is determined primarily by the genetic constitution of the population and the environment in which the phenotype is measured [36]. We will elaborate on how the genetic background of the population impacts the phenotypic effects of a QTL in later sections.

Unlike biparental segregant populations, in natural populations, a QTL may contain one or more alleles whose frequencies range from common to rare [34,37,38]. Usually, phenotypes of rare variants (less than 1% frequency) have a disproportionately more significant contribution to phenotypic variation and a substantially high heritability, therefore generating a phenotypic distribution such that individuals carrying a rare allele are at the extremes of the phenotypic spectrum [34]. If a large effect variant has a positive fitness effect on a phenotype, such a variant is ultimately

Glossary

Effect size: the magnitude by which a QTL causes a change in the phenotypic variance of a quantitative trait.
Hub loci: highly connected loci in genetic networks that are particularly conserved and pleiotropic. Modulatory hub loci can modulate the phenotypic effects of causal loci that are a part of the same genetic network as the hub locus.
Negative epistatic interactions: where deletion of a pair of genes leads to a higher fitness defect than the expected additive phenotypic effect due to single-gene deletions.
Phenotypic buffering: the ability of an organism or population not to show any significant phenotypic differences despite changes in the environment and changes in the genetic background.
Phenotypic plasticity: the ability of an organism or population to display different phenotypes across environments and due to changes in the genetic background.
Positive epistatic interactions: where deletion of a pair of genes leads to lesser fitness defect than expected additive phenotypic effect due to single-gene deletions.
Quantitative trait locus (QTL): region of the genome that contributes to the phenotypic variation in a quantitative manner. The phenotypic effects of these loci are generally dependent on the genetic background and the environment.
Reaction norm: environment-dependent phenotypic effects of genetic variants can be represented by reaction norms, which show the variation in the trait value (plotted on the *y*-axis) with a change in the environment (plotted on the *x*-axis).
Segregant: yeast segregants are haploid strains with unique genetic backgrounds generated as a result of a meiotic division of a diploid hybrid. Segregant populations are often generated *in vitro* to understand genetic interactions.

Key figure

Different experimental methods of identifying loci contributing to phenotypic plasticity

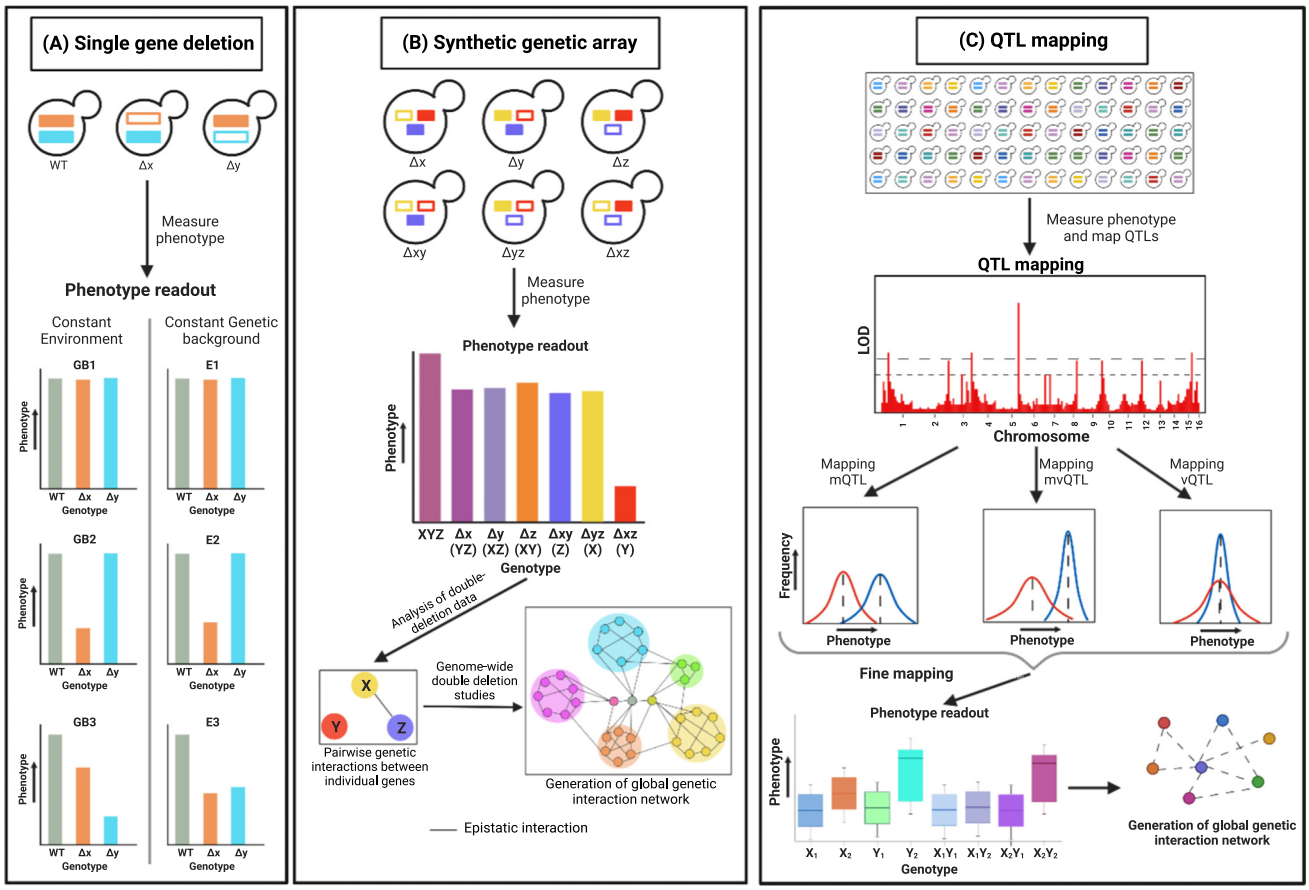

Figure 1. (A) Single-gene deletion studies can be used to identify the genetic background and environment-specific effects of additive loci in contributing to phenotypic plasticity. X and Y are two wild-type (WT) genes, which, when deleted, are indicated as Δx and Δy; GB1-GB3, genetic backgrounds, and E1-E3, environments. The graphs show the comparisons of phenotypes of gene deletion strains in multiple genetic backgrounds when the environment is constant (left) and across different environmental contexts when the genetic backgrounds are constant (right). Deletion of Δx or Δy in GB1 or E1 shows no additive effects. In contrast, in GB2 or E2, Δx shows a different phenotype compared with WT, so X has additive effects. In GB3 or E3, both Δx and Δy show a phenotype distinct from WT; therefore, X and Y have additive effects. (B) Synthetic genetic array (SGA) compares the phenotypes of single- and double-gene deletion strains. This method ascertains genetic interactions between a pair of genes. Here, X, Y, and Z are three genes. Comparison of phenotypic effects of single- and double-gene deletions show a genetic interaction between the pair X-Z and no interaction between pairs X-Y and Y-Z. Genes X and Z are observed to interact because the phenotypic value of their double deletion ΔxΔz is less than the additive value of the single deletions Δx and Δz. Systematic genome-wide double deletion of all genes can be used to construct global genetic interaction networks in different environments to observe the presence and range of phenotypic plasticity due to changes in genetic interaction networks. The shaded regions in the global genetic interaction network represent distinct subnetworks. These global genetic interaction networks can be used to identify genetic hubs, and the effects of genetic variation in rewiring the genetic networks, thereby driving phenotypic plasticity. (C) QTL mapping performed on natural or segregant populations leads to identifying multiple mean QTL (mQTL), variance QTL (vQTL), and mean-variance QTL (mvQTL). These QTLs can be fine-mapped to determine the role of causal loci in contributing to phenotypic plasticity in natural and segregant populations. Let X and Y be two causal genes, and X_1, X_2, Y_1, and Y_2 are alleles of these genes. Fine-mapping will identify that for mQTLs, only the phenotypic mean differs without a change in the variance. If X is an mQTL, the individuals carrying the X_1 allele have a mean phenotype lower than those with the X_2 allele. mvQTLs show both mean and variance differences. If Y is an mvQTL, the mean and variance phenotype of the individuals carrying the Y_1 allele is significantly different from those with the Y_2 allele. QTL mapping also enables the detection of QTL–QTL interactions; X_2Y_2 allelic pair has a higher mean and variance than the other three allelic pairs (X_1Y_1, X_1Y_2, X_2Y_1), indicating a genetic interaction between the X_2Y_2 alleles. These pairwise QTL–QTL interaction maps can be used to generate global genetic interaction networks. LOD, logarithm of the odds (LOD score is a statistical estimate of the relative probability that two loci, located near each other on a chromosome, are likely inherited together). Image created using BioRender.com.

fixed in a population [39]. However, a negative effect variant is maintained at a low frequency under selection pressure, resulting in an inverse relationship between effect size and allele frequency [40]. Due to random mating, natural populations have continual fluctuations in their allelic frequencies that display phenotypic plasticity under dynamic environments.

Nonadditive effects

Nonadditive loci involved in dominance and epistasis modulate the phenotype such that the phenotype deviates from the expected mean of the causal alleles. Because each individual has a unique genetic makeup, the genotypes of the interacting loci will be variable, causing the genetic interactions to alter with respect to the individual's genotype. Genotype-specific interactions in each cause phenotypic plasticity in the population [41]. Phenotypic buffering is observed when, despite the variable genetic interactions, homeostasis is maintained in the population, leading to lower phenotypic variation [42].

Effects of dominance on phenotypic plasticity

A significant contributor to the phenotypic effect of an allele across environments is the companion allele at the same locus. Both homozygous (37%) and heterozygous (63%) lineages are found in naturally occurring yeast strains, and the zygosity can have a substantial impact on the phenotype via interallelic interactions [24]. The difference in zygosities may result from mutations in the genome and sexual and asexual modes of reproduction driven by selection pressures [43,44]. In heterozygotes, the alleles can have a range of interactions from no dominance (phenotype is the average effect of both alleles) to dominance (phenotype is affected by either of the alleles) [45–48]. In plants, the degree of stability of a phenotype is proportional to the degree of heterozygosity of the causal loci, as the phenotype of the heterozygote is more robust [49,50]. This means that despite changes in the external environment, a loss of function or a deleterious phenotype is often not expressed in heterozygotes. The phenomenon of heterozygote advantage, where the heterozygotes are more robust than their homozygote counterparts, has also been observed in yeasts [49–52]. Heterozygote advantage could occur if one of the alleles in a heterozygote is nonfunctional and the other allele can compensate for the loss of function to maintain a robust phenotype. For example, the $MKT1^{89A}$ allele of S288c is a loss-of-function allele, but the effect is not seen in any heterozygotes with S288c as one of the parents [53–56].

In contrast, there would be a complete loss of function in a recessive homozygote. In addition, it was observed that the haploid progeny of a population derived from a heterozygous individual displays higher phenotypic plasticity because of the random segregation of alleles of the hybrid [33,41,52,57]. Regardless of the origin of haploid segregants, haploids display higher phenotypic plasticity than diploids because any mutation occurring in a haploid individual is not diluted or masked due to dominance effects occurring at the same locus. In diploids, if a *de novo* mutation is recessive but beneficial to the phenotype, the mutation's impact on the phenotype is not expressed due to a dominant allele at the same locus. But this dilution of phenotypic expression of heterozygous loci also makes diploids more robust to deleterious mutations [58]. A comprehensive study of the adaptive capabilities of haploids versus diploids is necessary to understand the benefits and drawbacks of both ploidy models.

Dominance, in most cases, is studied as an intralocus nonadditive effect; however, evidence shows that dominance effects can also be interlocus [33]. Whether it is intra- or interlocus, the results of dominance are observed when the effect of an allele is so strong that the impact of the other allele at the same or a different locus cannot be measured; that is, the dominant allele buffers the phenotypic effects of the rest of the alleles. However, the effects of the recessive alleles at the same or different locus can be detectable if the major buffering effect dominant allele is

eliminated or replaced by a recessive allele. This allows phenotypic expression of the recessive alleles, displaying phenotypic plasticity. One way to identify dominant loci contributing to a phenotype is by sequentially removing the major-effect loci [33]. Repeating such sequential elimination of the major QTL by the marker-based selection makes it easy to identify several QTLs with minor effects (interlocus dominance) with increased sensitivity. Furthermore, these studies found that the effects of interlocus dominance are genetic background dependent and profoundly connected to epistasis [28,33,59]. Large-effect genetic variants dominant across single or multiple loci can cause phenotypic buffering. Eliminating or silencing these dominant variants will lead to observable effects of the recessive loci, potentially leading to phenotypic plasticity.

Effects of epistasis on phenotypic plasticity

Several recent studies have unveiled the widespread impact of genetic interactions in regulating organismal phenotypes in individuals and across populations [60–63]. The definition of epistasis used in this review is that if the phenotypic effects of a particular pair of alleles across different loci deviate from the sum of their additive effects, it is known as 'epistasis.'

Epistasis is classically demonstrated by comparing single- and double-gene deletion effects on the phenotype. Suppose the impact of double-gene deletion is not equal to the additive effects of single-gene deletions; this pair of genes has an epistatic interaction (Figure 1B). Genome-wide double-deletion analysis of approximately 5000 genes via synthetic genetic array (SGA) performed in yeast in a nutrient-rich environment showed that out of the 23 million pairwise interactions, about 550 000 were **negative epistatic interactions**, and 350 000 were **positive epistatic interactions** [64]. Similarly, the deletion interaction network among the three genes was about 100 times larger than the pairwise deletion interaction network [65]. Therefore, as the number of genetic interaction partners increases, the complexity of the interaction network rises, thereby increasing the potential of these interaction networks to modulate the phenotype.

Role of genetic background as a modulator of phenotypic plasticity

The impact of causal additive and nonadditive loci on the phenotype is variable, as the phenotypic mean and variance are modulated, depending on the genetic background (Box 1) [66,67]. Although additive loci significantly affect the population phenotype independent of other loci, the phenotypic impact of additive loci varies across individuals with heterogeneous genetic backgrounds (Figure 1A) [36,68]. The modulatory effect of genetic background on the phenotype could be due to the loss or gain of function of the loci involved in that biological process [69]. The genetic background can thus act indirectly as a phenotypic plasticity modulator by causing differential penetrance or expressivity of the causal locus [2,70]. Furthermore, fundamental aspects such as the essentiality of a gene are also conditional on the genetic background. Of the 894 essential genes in Σ1278b and S288c strains, 44 were necessary only in the Σ1278b background and 13 genes in the S288c background [71]. The conditional essentiality of genes depends on the number of genetic background modifiers involved in modulating the causal locus [69].

Box 1. Impact of mQTL, vQTL, and mvQTL on the phenotypic landscape

The differential impact of a quantitative locus on a population's phenotype can be captured by mapping the mean versus variance QTLs (see Figure 1C in the main text) [126,127]. In an mQTL, the population subgroups containing different alleles of the causal locus have significantly different phenotypic means. However, in a vQTL, the population subgroups containing different alleles of the causal locus have differential phenotypic variance. These individuals containing one allele will show a buffered phenotype, where the influence of the genetic background or the environment to modulate the phenotype is minimal [41]. In contrast, individuals with the other allele at the causal locus will have a plastic phenotype displaying diverse phenotypic values [61,126,128,129]. Causal loci that impact a population's mean and variance are termed 'mvQTL' [85,126]. vQTL and mvQTL can cause phenotypic buffering or plasticity, depending on an individual's genetic background or, at a larger scale, the genetic composition of a population and the environment.

Similar to the relationship between additive phenotypic effects and the genetic background, the total contribution of dominance to the phenotype is also variable with respect to the genotype of the causal interacting loci and changes in the genetic background [45,66]. Mechanisms by which dominance relationships are modulated need to be better established, but proof of such modulation exists [48].

Genetic background-dependent epistatic interactions are also prevalent [72–76]. Although SGA is a tool widely used to study genetic interactions, techniques such as CRISPRiSeq and CRISPEY-BAR can examine differential epistatic interactions of essential genes in different genetic backgrounds [32,77]. The variable gene interactions in different genetic backgrounds lead to differential phenotypic effects, which can cause adaptive changes in populations. Pairs of genes whose allele-specific interactions result in beneficial phenotypes are selected over time, ultimately leading to the fixation of such alleles at different genomic loci. Along with the fixation of the beneficial variants, several genetic variants at neighbouring loci are also selected and fixed due to genetic hitchhiking [78]. In extreme cases, the mating of individuals of closely related species, whose alleles are fixed, can either display genetic incompatibility (reproductive isolation) [74,79,80] or generation of progeny with low hybrid vigour [81–83]. Poor fitness of hybrid progeny could result from detrimental epistatic interactions among novel combinations of alleles. These genetic and environmental context-dependent plastic effects of gene interactions drive speciation and evolution [27,80,82,84].

Role of the environment as a modulator of phenotypic plasticity

The ability of a QTL to display phenotypic plasticity depends on the environment in which the population adapts (Figure 1A). In specific environments, all genetic backgrounds display a buffered phenotype, whereas in other environments, a plastic phenotype is observed due to genotype–environment interactions. But an individual can exhibit a wide range of phenotypes across several environments (Figure 2). This environment-dependent phenotypic plasticity can be observed in the study where homozygous deletion of 93% of yeast genes impacts growth in at least 1 of 400 environments, demonstrating widespread additive effects of genes. However, about 90% of gene deletions impact growth in less than 20% of the environments, showing high environmental dependence and plasticity of these additive effects [29].

Similar to the role of genetic backgrounds on the population mean and variance, environmental changes can also modify the effects of QTLs by changing the mean and variance in an allele-specific manner, causing phenotypic plasticity (Box 1 and Figure 1C). Phenotypic buffering is observed when there is minimal variation in phenotype across different environments. An analysis of yeast segregants grown in 34 different environments showed that most of the QTLs mapped were mean QTL (mQTL), affecting only the phenotypic mean, with one-fourth of these mQTLs being mean-variance QTLs (mvQTLs), modulating both phenotypic mean and variance [85]. Compared to mQTL, variance QTLs (vQTLs), affecting the phenotypic variance, often have smaller effect sizes; thus, the mapping of a vQTL is restricted by statistical power. However, several studies have identified loci that differentially affect population variance across environments, implying the role of vQTLs in facilitating plasticity [21,85].

Causal loci depend not only on the environment but also on the genetic interactions within loci, such as dominance, and between loci, such as epistasis [26,37,66,80,86]. In a population of phased outbred lines that were phenotyped for fitness traits in nine physiologically different environments, the contribution of dominance to phenotypic variance ranged from 2% to 45% across environments [87]. This wide range of dominance contributions highlights the importance of the environment on dominance effects and, therefore, phenotypic plasticity.

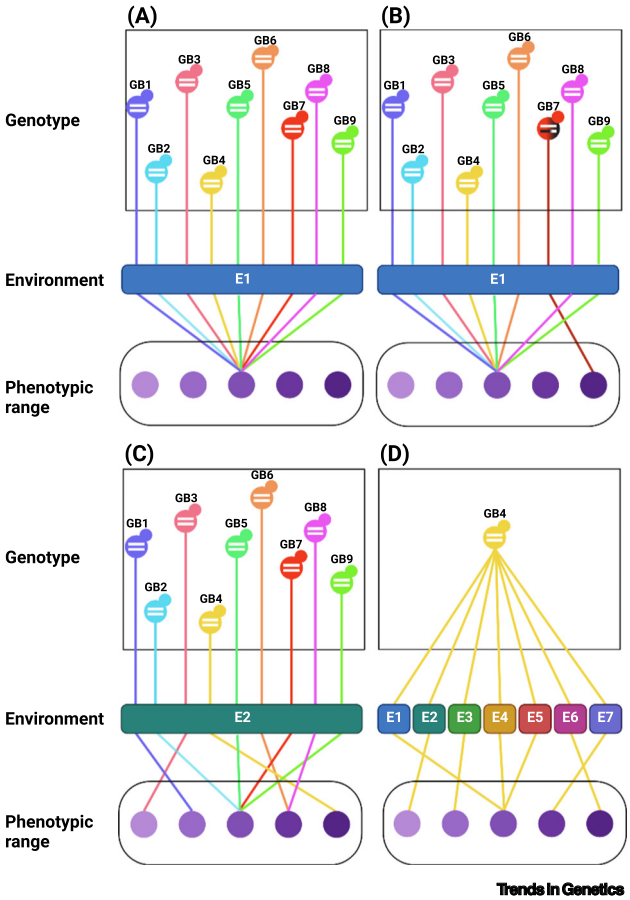

Figure 2. Representation of phenotypic plasticity due to genetic and environmental variation. GB1-GB9 are varying genetic backgrounds, and E1-E7 are different environments. The phenotypic range represents variable fitness. (A) Individuals of a population display the same phenotypic value, regardless of unique genetic backgrounds in environment E1 displaying a buffered phenotype. (B) A mutation in one of the individuals (GB7) of the population can lead to a change in its phenotype, deviating from the wild-type phenotype. This represents the origin of phenotypic plasticity due to minor changes in the genetic background, even though there is no variation in the environment. (C) Individuals of the same population, when subjected to growth in E2, have different phenotypic values, depending on the genetic backgrounds, displaying phenotypic plasticity. (D) An individual strain with a constant genetic background (GB4) displays phenotypic buffering and plasticity, depending on its environment. In environments E1, E4, and E5, a buffered phenotype is observed; in contrast, in E2, E3, E6, and E7, a plastic phenotype is observed. Image created using BioRender.com.

In the case of epistatic interactions, environment-specific genetic interactions can be studied by performing assays such as SGA across different environments [64]. Epistatic interactions show environmental dependence; when 257 000 epistatic interactions were tested, 32% showed differential interactions across five environmental conditions [75]. However, in another recent study where almost double the number of genetic interactions (420 000) were tested across 14 environments, only 12% showed differential interactions [75]. The first study on the mitogen-activated protein kinase pathway genes observed a higher proportion of differential interactions as signalling pathway genes are likely to have more interactions and show higher plasticity than the second one, which included all major yeast bioprocess genes [75,88]. Studies also indicate that gene–gene interactions are more abundant than gene–gene–environment interactions [89–93]. This condition-specific differential effect of genetic interactions on the phenotype causes phenotypic plasticity or buffering [6].

A buffered phenotype may neither positively nor negatively impact the populations when the external environmental conditions are constant. However, in scenarios with drastic environmental changes, these buffered individuals may be less equipped to survive than individuals with phenotypic plasticity. Both phenotypic plasticity and buffering occur due to complex and variable gene–gene and gene–environment interactions [41,42].

Modulation of phenotypic plasticity by genetic networks

Pairwise and higher-order (involving more than two loci) genetic interactions can be concatenated to form large genetic networks. Modulation of network properties of these genetic networks can drive change in the phenotype. The phenotypic effect size of all the loci in a genetic network depends on the genotype of the interacting loci [94], the genetic background [72,95], and the environment [8,96]. These three parameters can change the network topology and its impact on the phenotype [21,86,97]. Despite dynamic changes in the wiring of a genetic network due to the genetic and environmental backgrounds, the overall network properties remain conserved; for example, genes of a specific molecular function or pathway are highly likely to interact amongst themselves across populations [69,73,85,91,98,99]. Variations in the genotype, genetic background, or environment can lead to the loss or gain of genetic interactions in a genetic network. The *RME1* gene has genetic background–dependent interactions for the sporulation efficiency of yeast. In oak and vineyard strains, it interacts with *IME1* and *RSF1*, whereas in laboratory and soil strains, it interacts with *MKT1* and *TAO3* [100]. Such changes in the effect sizes, loss or gain of interactions, and change in the direction of interaction (positive or negative genetic interactions) with variation in the genetic and environment impact phenotypic plasticity [26,80,86,99,101].

In genetic networks, highly connected loci, which often form the 'hubs,' are highly conserved and pleiotropic [21,102,103]. Some of these **hub loci** act as modulators of phenotypic plasticity by aiding or buffering the phenotypic manifestation of loci epistatically interacting with them [97,103]. Genetic variation in the modulatory hub loci has a higher potential to affect the fitness of several connected loci than in other nonhub loci [85]. This was observed in several six-locus genetic networks where the genotype of the hub locus determined whether the phenotype would be plastic or buffered [21]. The study considered the same interaction network with different genetic variants at each locus. Although each combination of genetic variants had a distinct phenotype, there was a significant difference in the mean and variance of the networks when the hub locus varied [21]. Another example of phenotypic modulation due to variation at the hub locus can be observed in the case of the protein-folding chaperone *HSP90*. The replacement of *HSP90* in *S. cerevisiae* with an ortholog from *Yarrowia lipolytica*, a subspecies of yeast adapted to growth in hypersaline environments, resulted in fitness defects in normal growth conditions, whereas in hypersaline growth conditions, the *Yarrowia* ortholog conferred better growth than the native one [104]. This study indicates that changing the genotype of the modulatory hub locus *HSP90* from a normal saline–adapted *HSP90* ortholog to a hypersaline-adapted *HSP90* ortholog causes genetic network rewiring, leading to different phenotypic impacts, depending on the environmental context [104]. Such studies prove that variation in the hub locus can lead to higher phenotypic plasticity than variations in the other interacting genes, even though the latter is more frequently observed in nature [102].

A bias for lower genetic variation at the highly connected hub loci could be a result of the potentially high costs of phenotypic variation at the hub compared with other loci [105–108]. The phenotypic manifestations of genetic variation at the hub locus are significant and could have both a positive adaptive effect and a negative detrimental effect. Therefore, a perturbation in the interactions between the hub and the nonhub loci can be involved in several molecular processes leading to the modulation of multiple phenotypes, ultimately affecting the fitness of the organism.

Because of the significant impact of the hub locus on phenotypic plasticity, variations at this locus drive evolutionary changes at a much faster rate than variations at other loci [107]. Conversely, due to variation in the modulatory hub locus, specific loci whose phenotypic impact was suppressed until now became causal to affect the phenotype significantly. The phenotypic impact of such genetic variation that was earlier buffered is known as the release of cryptic genetic variation (CGV) [30,109]. CGV is generated due to the loss of fidelity of DNA repair mechanisms. Genetic modulators buffer CGV against most genetic and environmental perturbations such that the organism's phenotype is invariable [10–12,110,111]. But under specific genetic and environmental contexts, the CG variants act as mvQTLs, leading to extreme phenotypes (Figure 2B), potentially aiding in adaptations to novel environments [85,109,112]. Environment-dependent release of CGV can lead to a sizeable phenotypic impact and potentially contribute to phenotypic plasticity and adaptation. Beneficial CGV is ultimately fixed in evolution, resulting in the genotypic variation and, thus, a change in the phenotypic mean [109].

Concluding remarks and future directions

The genetic architecture of genes and their interaction networks forms the basis of phenotype and phenotypic plasticity. Phenotypic plasticity in populations is observed because of the unique genetic makeup of each individual in the population, leading to variable phenotypes. Causal loci can have both additive and nonadditive phenotypic effects that are variable with respect to the genotype of the causal loci, the genetic background, and the environment. Loci can cause phenotypic variation by acting as mQTL, vQTL, or mvQTL. Individuals carrying vQTLs and mvQTLs display phenotypic plasticity and are more adaptive to drastic environmental changes than individuals with a buffered phenotypic spectrum. Release of CGV occurs when there is a variation at the modulatory hub locus or changes in the genetic background or the environment.

As discussed herein, the genetic architecture of an organism is complex, wherein genetic interactions and their ability to contribute to a phenotype are dynamic, depending on the genetic and environmental background [41,76,97,113]. This complex and differentially receptive genetic architecture results in a nonlinear relationship between the genotype and the phenotype, making phenotype prediction challenging [69,72] (see Outstanding questions). Prediction of phenotype is essential to understanding the effects of beneficial and deleterious genetic variants, generating high-yielding commercial yeast strains and estimating yeast's fitness and impact in clinical scenarios. Several fine-mapping studies of the yeast genome use additive, dominance, and epistatic genetic models to predict phenotype [8,21,114–117]. However, most of these studies do not account for all the variants that contribute to the phenotype but rather apply prediction models only to a subset of additive loci. Thus, despite these fine-mapping studies, an accurate prediction has not been achieved, indicating the contribution of nongenetic elements to the phenotype.

Several nongenetic factors contribute to a phenotype, including the spatiotemporal activity of a cell, intracellular stochasticity, and epigenetic modifications, to name a few [118]. The differential spatiotemporal activity of a cell involves the growth phase, the age of the cells, and the molecular dynamics of a cell that play a role in the phenotypic plasticity [119,120]. This can even be observed in metazoans; for example, the foetal and adult gene expression programs in the cardiac muscle are unique, indicating differences in phenotype due to the different developmental stages. However, after myocardial infarction in adults, a difference in the microenvironment of the cardiac cells results in the re-expression of the foetal gene expression program [121]. Intracellular stochasticity results in phenotypic plasticity in individuals of a clonal population in an environment due to uneven distribution of macromolecules or cell organelles such as mitochondria during cell division and bursts of transcription [4,42,122–124]. In metazoans, a phenotype is modulated by several other factors, such as tissue microenvironments, signalling cues, and fluctuating

Outstanding questions

What properties of a locus make it a regulator of phenotypic plasticity or buffering?

How does a locus switch roles between phenotypic plasticity or buffering regulator, based on the genetic and environmental contexts?

Are all neutral variants in the genome potential cryptic genetic variants?

How is phenotypic plasticity balanced by mechanisms such as antagonistic pleiotropy and phenotype trade-offs, where one trait has increased phenotypic value at the expense of a decreased phenotypic value of another trait? Does trade-off across multiple phenotypes affect the overall fitness of an individual?

How can we integrate multiomic data to identify molecular processes that drive phenotypic plasticity through evolution?

Although several studies identify phenotypic variation without the label of plasticity or buffering, there needs to be a holistic understanding of how these mechanisms lead to changes in the genome and help in short- and long-term adaptation. There is a need to experimentally identify the role of phenotypic plasticity in driving evolutionary processes.

asymmetry. These nongenetic contributions to the phenotype are represented as higher variance in the phenotype on a **reaction norm**. Although nongenetic factors contribute to phenotypic modulation, the impact of genetic factors on phenotypic plasticity is higher.

It is necessary to understand the patterns of genetic interactions, their effects on the phenotype, and the mechanisms by which phenotypic plasticity and buffering are brought about [80,125]. For that reason, apart from using exhaustive genetic models for phenotype prediction, studies such as single-cell transcriptomics and proteomics can help us better understand the intracellular dynamics at a higher resolution. Multiomic data can provide the links between each stage of phenotypic manifestation, starting from gene expression, to better understand the modulators and the mechanisms of modulation of phenotypic plasticity in real time. An accurate prediction of phenotype can assist in determining short- and long-term responses to selection, generation of robust strains, and disease prediction and severity.

Acknowledgments

We acknowledge support from the Exploratory Research Project grant from IIT Madras (BIO/17-18/867/RFER/HIMA) to H.S. and the consultancy project from Excelra Knowledge Solutions Private Limited (CR/22-23/0026/BT/EXCE/008752) to H.S. Figures were created with BioRender.com.

Declaration of interests

No interests are declared.

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